Is the Consensual Threshold for Defining High Glucose Variability Implementable in Clinical Practice?

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OBJECTIVE

Estimating glycemic variability (GV) through within-day coefficient of variation (%CV$_w$) is recommended for patients with type 1 Diabetes (T1D). High GV (hGV) is defined as %CV$_w$ > 36%. However, continuous glucose monitoring (CGM) devices provide exclusively total CV (%CV$_T$). We aimed to assess consequences of this disparity.

RESEARCH DESIGN AND METHODS

We retrospectively calculated both %CV$_T$ and %CV$_w$ of consecutive T1D patients from their CGM raw data during 14 days. Patients with hGV with %CV$_T$ >36% and %CV$_w$ ≤36% were called the "inconsistent GV group".

RESULTS

A total of 104 patients were included. Mean ± SD %CV$_T$ and %CV$_w$ were 42.4 ± 8% and 37.0 ± 7.4% respectively ($P < 0.0001$). Using %CV$_T$, 81 patients (73.6%) were classified as having hGV, whereas 59 (53.6%) using %CV$_w$ ($P < 0.0001$) corresponding to 22 patients (21%) in the inconsistent GV population.

CONCLUSIONS

Evaluation of GV through %CV in patients with T1D is highly dependent on the calculation method and then must be standardized.

Glycemic variability (GV) refers to the swings in blood glucose levels. High GV (hGV), particularly observed in type 1 diabetes (T1D) (1), is linked to the pathogenesis of diabetes long-term complications and to the risk of severe hypoglycemia (2,3). It is then crucial to well identify patients with hGV. Several metrics could be used to evaluate GV—assessing either its amplitude or its timing (4). An international consensus proposed that the coefficient of variation (%CV) of glucose concentrations, assessed by continuous glucose monitoring (CGM), should be the estimate of GV used, with SD of glucose as a secondary estimate (5). For a given period, several SDs can be computed. SD of glucose concentrations during the total period (SD$_T$) (SD for all of the data) includes both the within-day (SD$_w$) (mean SD of all of the measurements in a 24-h period) and the between-day (SD$_b$) (mean SD over all days at a specified time) variability (6). The %CV is determined by the formula ([SD] / [mean glucose]) × 100, in which glucose SD can correspond to these different situations, giving different %CV: %CV$_T$ ([SD$_T$] / [mean glucose] × 100), %CV$_w$ ([SD$_w$] / [mean glucose] × 100), and %CV$_b$ ([SD$_b$] / [mean glucose] × 100). Recently, international recommendations (5) proposed to define hGV as %CV$_w$

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NOVEL COMMUNICATIONS IN DIABETES

>36%, evaluated over a period of at least 14 days, based on a previous study that observed that the number of hypoglycemia events was significantly higher above this threshold (7). SD was computed according to the SD_w definition; therefore, 36% refers to %CV_w. Data from CGM could easily be downloaded from websites, such as LibreView (for FreeStyle Libre: https://www.libreview.com) or Dexcom CLARITY (for Dexcom: https://clarity.dexcom.eu), helping physicians and patients to interpret GV and adapt insulin doses. In contrast with the international recommendations (5), the one %CV automatically given by these websites is %CV_T. The aim of this study was to highlight the potential issues induced by this disparity for patients with T1D.

RESEARCH DESIGN AND METHODS
Study Design and Participants
Consecutive patients with T1D who uploaded their data from the FreeStyle Libre system to their LibreView account between February and April 2019 were retrospectively screened. Those with >70% of CGM active time for the last 14 days were included. For each patient included, information regarding age, sex, diabetes duration, severe hypoglycemia incidence in the last 6 months, and HbA_{1c} were collected.

In light of the noninterventional design of this retrospective study, all participants gave oral or written informed consent (inclusion in Middlecare register or nonopposition note) for the use of records for clinical research purposes.

Analysis of the Data From the CGM
Total glycemic report (one measurement per 15 min) for the last 14 days was downloaded in a .csv file per patient; %CV_T and %CV_w were calculated according to the following equations:

$$SD_w = \frac{\sqrt{\frac{\Sigma|x-\bar{x}_{j1}|^2}{(n-1)_{j1}}} + \sqrt{\frac{\Sigma|x-\bar{x}_{j2}|^2}{(n-1)_{j2}}} + \cdots + \sqrt{\frac{\Sigma|x-\bar{x}_{j14}|^2}{(n-1)_{j14}}}}{14}$$

$$SD_T = \sqrt{\frac{\Sigma|x-\bar{x}_{j14}|^2}{(n-1)_{j14}}}$$

$$\%CV_T = [SD_T]/[14 \text{ days mean glucose}] \times 100$$

$$\%CV_W = [SD_W]/[14 \text{ days mean glucose}] \times 100$$

Patients were classified into three groups: group 1, the "constantly low GV group" for patients with both %CV_T and %CV_w ≤36%; group 2, the inconsistent GV group for patients with %CV_T >36% but with %CV_w ≤36%; and group 3, the "constantly high GV group" for patients with both %CV_T and %CV_w >36%. No patients had %CV_T <36% but %CV_w ≥36%; this group was therefore not considered. Characteristics of these three groups were then compared.

Statistical Analysis
Variables with normal distribution are expressed as mean ± SD, and others are expressed as median (quartile 1–quartile 3). Comparisons of means were made with Mann-Whitney U tests and comparisons of proportions with χ^2 tests. A Spearman rank correlation test was performed to study the correlation between %CV or hypoglycemia parameters and time below range (TBR) or hypoglycemia incidence. Mann-Whitney U tests, χ^2 tests, and Spearman rank correlation tests were performed with use of GraphPad Prism, version 8.0.0 for Windows (GraphPad Software, San Diego, CA).

RESULTS
A total of 104 patients was included, 42% of whom were men, with mean ± SD age 44 ± 15 years, diabetes duration 25.5 ± 13.5 years, and HbA_{1c} 7.3% ± 1% (56 mmol/mol). Median SD_T and SD_w were, respectively, 72.1 mg/dL (4 mmol/L) and 62.9 mg/dL (3.49 mmol/L) ($P < 0.0001$). Mean %CV_T and %CV_w were 42.4 ± 8 and 37.0 ± 7.4% ($P < 0.0001$) (Fig. 1A).

Both %CV_T and %CV_w were significantly ($P < 0.0001$) correlated with TBR, <70 mg/dL (r_{CVT} = 0.60; r_{CVw} =

0.61). Neither SD_T nor SD_w was significantly correlated with incidence of hypoglycemia or TBR (see Supplementary Table 1). Correlations between TBR and other GV or hypoglycemia parameters are indicated in Supplementary Fig. 1 and Supplementary Table 1.

Using %CV_T, 81 patients (73.6%) were classified as having high hGV, and 59 (53.6%) were classified as having high hGV using %CV_w ($P < 0.0001$). A total of 23 patients (22%) were in group 1, 22 (21%) in group 2, and 59 (57%) in group 3. In group 2, the number of hypoglycemia events and the TBR were significantly lower in comparison with group 3 and significantly higher in comparison with group 1 (Supplementary Table 2).

%CV_T was systematically greater than %CV_w, with a median difference of 5.2% (Fig. 1B). Incidence of hypoglycemia and TBR were significantly higher in patients with %CV >36%, whatever the formula used ($P < 0.0001$ for both). An ROC curve showed that 36% and 41% were the best thresholds for predicting TBR for %CV_w and %CV_T, respectively (Supplementary Fig. 2).

CONCLUSIONS
The evaluation of GV through %CV is dependent on the calculation method: we found a significant difference between %CV_T and %CV_w. Since SD_T includes both SD_w and SD_b (6), the differences observed between SD_T and SD_w (and between %CV_T and %CV_w) are due to the contribution of SD_b. As SD_b is by definition >0 (8), %CV_T is always above %CV_w.

Because of this difference, 20% of our patients with T1D are classified as having low GV and having hGV depending on the SD used for %CV calculation. The two consequences of this difference are as follows: 1) It is crucial to standardize the calculation method of %CV for evaluation of GV. 2) All studies with evaluation of GV through %CV should specify which %CV is used.

Whatever the means of calculation, %CV was positively correlated with TBR, consistent with previous studies (2,7,9–11), even though incidence of hypoglycemia is also known to be a function of mean glycemia (4,11). However, %CV is a metric of GV
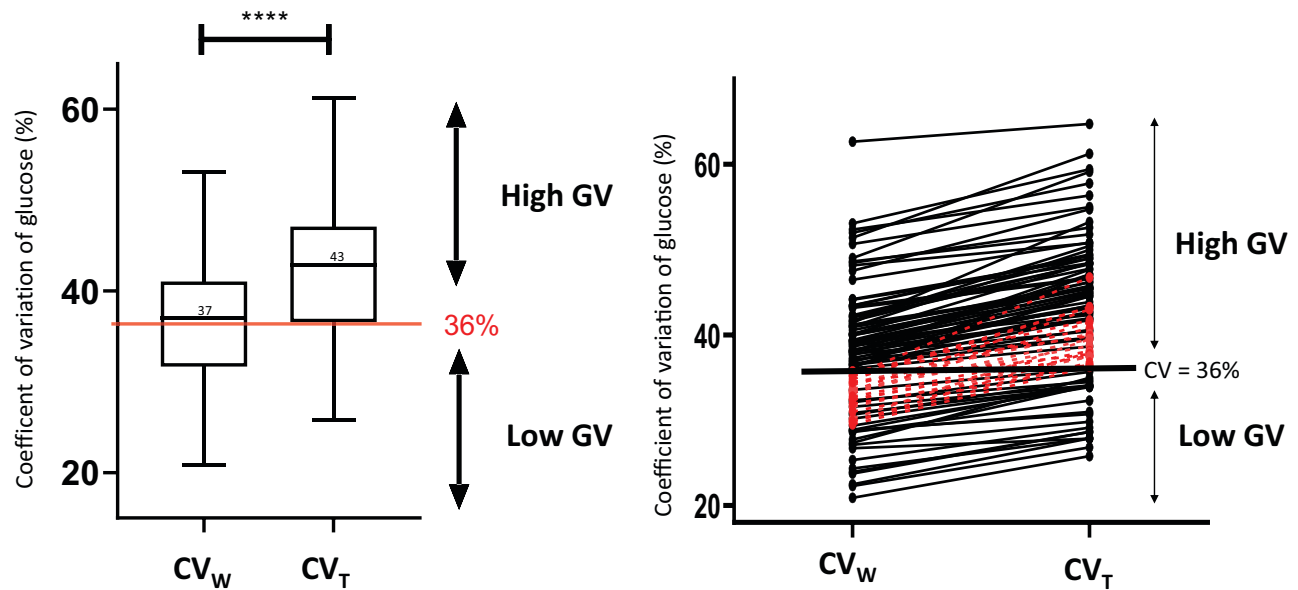
Figure 1—Comparison of %CV$_w$ and %CV$_T$ in consecutive patients with type 1 diabetes. Box plot of %CV (*A*) and corresponding %CV for each patient (*B*) according to the method of calculation. ****$P < 0.0001$. CVs refer to CVs of glucose. CV$_w$ is recommended for assessment of GV, and CV$_T$ is given in LibreView and Dexcom CLARITY.

based on both glucose values below and glucose values above target range and, as confirmed in our study, is less effective in evaluation of the risk of hypoglycemia than specific hypoglycemia indices such as the low blood glucose index (LBGI) (12), which are only based on the glucose values below target (Supplementary Fig. 1 and Supplementary Table 1).

In our cohort, patients with consistently high CV have higher incidence of hypoglycemia events in comparison with other groups. These patients are considered as hGV on the basis of %CV$_w$ with a threshold at 36% and constitute 56% of our population with T1D, consistent with the findings of Monnier et al. (7).

In clinical practice, GV assessment should help with identification of patients at risk for severe hypoglycemia. According to the 36% threshold, a high proportion of our population was classified as hGV: 54% on the basis of %CV$_w$ or 74% based on %CV$_T$. Considering that 31.5%–40.5% of subjects with T1D have severe hypoglycemia, (13–15), the large proportion of hGV-classified patients shows the limit of using the %CV$_{(w \text{ or } T)}$ 36% threshold to evaluate severe hypoglycemia risk.

Prospective studies are needed to determine which aspect of GV (i.e., %CV$_T$, %CV$_w$, %CV$_b$, mean amplitude of glycemic excursion, or LBGI, etc.) and which thresholds of these parameters are the best indices for prediction of severe hypoglycemia risk in patients with T1D, for a given mean glycemia.

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